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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/731,256	12/09/2003	John Gavin MacDonald	KCX-859 (19100)	4720

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SCHLIENTZ, NATHAN W	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/731,256	MACDONALD ET AL.	
	Examiner	Art Unit	
	Nathan W. Schlientz	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 September 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28,30,31,33-47,49,50 and 52-61* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28,30,31,33-47,49,50 and 52-61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 14 September 2007 has been entered.

Status of Claims

Claims 29, 32, 48 and 51 have been cancelled and claims 28 and 47 have been amended in an Amendment filed 14 September 2007. As a result, claims 28, 30-31, 33-47, 49-50 and 52-61 are pending and thus examined herein on the merits for patentability. No claim is allowed at this time.

Response to Arguments

Applicant's Remarks filed 14 September 2007 have been fully considered but they are not persuasive for the reasons set forth herein below.

Withdrawn Rejections

1. The objection to claim 32 under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim is hereby **withdrawn** by the examiner in light of the aforementioned cancellation of the instant claim.

2. The rejection of claims 28, 30-47 and 49-61 under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent Application Publication No. 2003/0082237 (Cha et al.) in view of The Merck Index is hereby **withdrawn** by the examiner in light of the aforementioned claim amendments wherein the functional compound is bonded to alumina on the surface of the nanoparticle. The functional compound of Cha et al. are encapsulated within the inner layer of the nanoparticle sphere and released when the particles are opened in response to environmental conditions.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. Claims 28, 30-31, 33-47, 49-50 and 52-61 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Specifically, the instant claims are drawn to a method of utilizing a triggerably releasable delivery system in "***the treatment of a patient***". However, the instant claim does not define what condition the patient is being treated against, and nor does the instant specification define "***the treatment of a patient***" to consist of specific conditions.

Also, the instant claims are drawn to nanoparticles containing silica coated with alumina, which provides a site on a surface of the nanoparticles to which is bonded "***a functional compound***". The specification, while providing the examples of hydrocortisone, tetracycline, ascorbic acid, aspartame, baicalin hydrate, baicalein, daunorubicin, salicylamide, salicylanilide, salacetamide, salsalate, albofungin, phenylalanine, salicylaldehyde and salicylaldoxime, does not reasonably provide support for all functional compounds.

Finally, the instant claims are drawn to nanoparticles which release the functional compound from the surface upon exposure to "***an environmental or chemical condition***". The specification only provides examples of changing pH resulting in the release of hydrocortisone, tetracycline, salicylaldehyde, and salicylaldoxime from the particle. Therefore, the instant specification does not reasonably describe the instantly claimed invention in a manner that would enable a person skilled in the art to make and use the invention as presently claimed.

2. Claims 28, 30-31, 33-47, 49-50 and 52-61 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. In particular, the instant claims are drawn to nanoparticles containing silica coated with alumina, which provides a site on a surface of the nanoparticles to which is bonded "a functional compound". However, the specification is not enabling for all functional compounds. Similarly, claims 33-34 and 52-53 are drawn to the functional compound being an anti-microbial agent, anti-viral agent, or therapeutic agent. The specification is not enabling for all anti-microbial, anti-viral, and therapeutic agents.

Attention is directed to In re Wands, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing Ex parte Forman, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

1) the nature of the invention
2) the state of the prior art
3) the relative skill of those in the art
4) the predictability of the art
5) the breadth of the claims
6) the amount of direction or guidance provided
7) the presence or absence of working examples
8) the quantity of experimentation necessary

The instant specification fails to provide guidance that would allow the skilled artisan to practice the instant invention without resorting to undue experimentation, as discussed in the subsections set forth herein below.

The nature of the invention

The claimed invention relates to a method of utilizing a triggerably releasable delivery system in the treatment of a patient comprising administering a plurality of nanoparticles containing silica coated with alumina, which provides a site on a surface of the nanoparticles to which is bonded a functional compound which is released from the surface upon exposure to an environmental or chemical condition.

The predictability of the art

It is difficult to predict the ability of all compounds to bind to the surface of an alumina-coated nanoparticle and then be released upon exposure to an environmental or chemical condition. Various structural differences in compounds lead to various physical and chemical properties that make it difficult to predict the efficacy of each compounds ability to bind said nanoparticles.

The breadth of the claims

The claims are very broad in that they are drawn to any functional compound.

The amount of direction or guidance provided

The instant specification does not provide guidance with respect to all functional compounds, and the process for binding all functional compounds to the alumina-coated surface of the claimed nanoparticles.

The presence or absence of working examples

The instant specification provides examples of tetracycline, daunorubicin baicalin hydrate, baicalein, ascorbic acid, phenylalanine, hydrocortisone, salicylaldehyde, and salicylaldoxime being adsorbed to the alumina surface of said nanoparticles.

The quantity of experimentation necessary

It would require undue experimentation for a person of ordinary skill in the art to determine the ability of all functional compounds to bind to the alumina surface of said nanoparticles, followed by release upon exposure to an environmental or chemical condition.

Therefore, for the aforementioned reasons, the Applicant is not reasonably enabled for all functional compounds.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

1. The rejection of claims 28, 30-31, 33-38, 40 and 45 under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No. 6,007,795 (Masterman et al.) is hereby **maintained** for the reasons of record in the Office Action mailed 14 May 2007.

Response to Arguments

Applicant's argue on page 8 of the aforementioned Remarks that claim 28 expressly requires that the alumina provides a site on the "surface" of the nanoparticles to which is bonded the functional compound, and if the anti-microbial agent of Masterman et al. were bonded to a surface of the particle, it would be immediately exposed and released to the mouth of a patient, thereby completely vitiating the

purpose of the "degradable material" to controllably release the agent only upon disruption of the water-stable coating and subsequent contact of the degradable material with saliva.

However, the examiner respectfully directs attention to column 5, lines 39-45, wherein Masterman et al. teach immediate release of a portion of the degradable material upon administration to the mouth and additional release by degradation after exposure to enzymes. Therefore, immediate contact of the active agent bound to the degradable material with the mouth cavity does not vitiate the purpose of the "degradable material", but is actually taught by Masterman et al. as a viable step in the invention. Also, when the degradable material is bound to both the minerals (column 3, lines 54-60) and the anti-microbial agent (column 4, lines 64-67), which is then coated on the particle, at least a portion of the anti-microbial agent will be present on the surface of the degradable material. Therefore, the composition of Masterman et al. will have a portion of anti-microbial bound to alumina on the surface of the particle, which is released when introduced into the oral cavity.

Applicants argue on pages 8 and 9 that Masterman et al. fails to disclose the zeta potential of the nanoparticles. However, the Office does not have the facilities for examining and comparing applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same functional characteristics of the claimed product. The zeta potential of the nanoparticles is descriptive and thus would be an inherent property of the claimed composition. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the

claimed products are functionally different than those taught by the prior art and to establish patentable differences. See *Ex parte Phillips*, 28 U.S.P.Q.2d 1302, 1303 (PTO Bd. Pat. App. & Int. 1993), *Ex parte Gray*, 10 USPQ2d 1922, 1923 (PTO Bd. Pat. App. & Int.) and *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in Graham v. John Deere Co., 383 U.S. 1,148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

1. Claims 39, 41-43, 47, 49-50 and 52-60 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,007,795 (Masterman et al.) in view of Ma, Bansal and Clark, Fundamentals of Adsorption, 1992, 80: 17-22 (Ma et al.).

Applicant claims:

Applicants claim a method of claim 28 wherein the environmental or chemical condition includes a change from acidic to alkaline pH or a change from alkaline to acidic pH.

Determination of the scope and content of the prior art

(MPEP 2141.01)

Masterman et al. teach a particle comprising an anti-microbial agent, such as tetracycline (column 2, line 20), attached to a particle coating, or skin, composed of a degradable material (column 4, lines 64-67), wherein the degradable material comprises polymers or monomeric species (column 3, lines 29-53) mixed or covalently bound with minerals such as silica and alumina (column 3, lines 54-67). Masterman et al. further teach that the degradable material can also act as the water-stable exterior (column 2, lines 1-6). Masterman et al. teach that the anti-microbial agent is released from the particle when the particle is placed in the mouth of a patient as a result of enzymatic degradation, or chewing or brushing (column 5, lines 33-55).

Ascertainment of the difference between the prior art and the claims

(MPEP 2141.02)

Masterman et al. do not explicitly teach anti-microbial agent to be released upon a change in pH. However, Ma et al. teach absorption of tetracycline on alumina is pH dependent, wherein the amount of tetracycline absorbed on the alumina reduces with a change to alkaline or acidic pH (Abstract; page 389, lines 7-8 of the Introduction; page 391, lines 1-6 of the Results and Discussion; Figures 1 and 2; and Table 1).

Finding of *prima facie* obviousness

Rational and Motivation (MPEP 2142-43)

Therefore, it would have been *prima facie* obvious for one skilled in the art at the time of the invention to prepare the nanoparticles of Masterman et al. coated with silica and alumina, to which is attached a functional group, such as tetracycline, which is released upon a change to alkaline or acidic pH, as reasonably taught by Ma et al.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

2. Claims 28, 30-31, 34 and 36-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,548,264 (Tan et al.).

Applicant claims:

Applicants claim a method comprising administering to a patient a plurality of nanoparticles containing silica coated with alumina that are about 500 nm or less, wherein the alumina provides a site on a surface to which is bonded a functional compound that is released in response to exposure to an environmental or chemical condition, and the nanoparticles possess a zeta potential of about 20 mV or more.

Determination of the scope and content of the prior art

(MPEP 2141.01)

Tan et al. teach silica-coated nanoparticles, wherein the nanoparticles comprise a core coated with a shell, such as mixtures or layers of silica and alumina, and derivatized with functional groups on the surface thereof, which can be used as drug molecule particles (Figure 1; column 2, lines 9-14 and 24-25; column 5, lines 55-60 and 67; column 6, lines 1-4 and 36-44; and column 11, line 62 through column 12, line 1). Tan et al. further teach that the nanoparticles are preferably between about 10 nm to about 300 nm (column 4, lines 26-35), and can be dispersed in a pharmaceutically acceptable carrier and administered to a patient (column 12, lines 1-4). Also, Tan et al. teach that drugs coated onto the nanoparticles can be further contained within a time-release coating (i.e. biodegradable sugar) so that the drug can accumulate at the site before becoming active (column 12, lines 7-10).

Ascertainment of the difference between the prior art and the claims

(MPEP 2141.02)

Tan et al. do not explicitly teach nanoparticles containing silica coated with alumina wherein the nanoparticles possess a zeta potential of about 20 mV or more. However, Tan et al. do teach that the nanoparticles comprise a shell that can be composed of an inorganic oxide such as alumina or silica, or mixtures of the foregoing, and the shell can include a first layer of silica coating and immediately adjacent to the core, and a second layer coating the silica layer (column 5, lines 55-60 and 67; and column 6, lines 1-4).

With regard to the zeta potential of the nanoparticles of Tan et al., the nanoparticles of Tan et al. are comprised of the same materials as the instant claims, and thus they would possess the same zeta potential as the instantly claimed nanoparticles. The examiner respectfully points out the following from MPEP 2112: "The discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." *Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Thus the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. *In re Best*, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977). In *In re Crish*, 393 F.3d 1253, 1258, 73 USPQ2d 1364, 1368 (Fed. Cir. 2004), the court stated that "just as the discovery of properties of a known material does not make it novel, the identification and characterization of a prior art material also does not make it novel."

Finding of *prima facie* obviousness

Rational and Motivation (MPEP 2142-43)

Therefore, it would have been *prima facie* obvious for one skilled in the art at the time of the invention to make the nanoparticles of Tan et al. comprising a core coated with a shell that is functionalized with a chemical or biological group and administering the nanoparticles to a patient, wherein the shell comprises silica coated with alumina, as reasonably taught by Tan et al.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

3. Claims 28, 30-31, 33-47, 49-50 and 52-61 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,785,977 (Breithbarth) in view of U.S. Patent No. 6,548,264 (Tan et al.).

Applicant claims:

Applicants claim a method comprising administering to a patient a plurality of nanoparticles containing silica coated with alumina that are about 500 nm or less, wherein the alumina provides a site on a surface to which is bonded a functional compound that is released in response to a change in pH, and the nanoparticles possess a zeta potential of about 40 mV or more.

Determination of the scope and content of the prior art

(MPEP 2141.01)

Breithbarth teaches silica or alumina microparticles, the surface of which is able to complex with a pharmaceutical agent by ionic bonding (column 2, lines 31-39 and 58-59). Breithbarth teaches that silica particles can be used directly or modified by coating or chemically bonding an active phase onto the silica particle's surface (column 3, lines 20-22). Also, Breithbarth teaches that a change in pH may affect the microparticles

charge, and thus its ability to bind the desired target (column 2, line 64 through column 3, line 1). Furthermore, Breithbarth teaches the particles may be administered topically, parenterally, orally, rectally, or vaginally (column 1, lines 64-66), and can be applied as a liquid, gel, cream or spray (column 3, lines 60-65).

Ascertainment of the difference between the prior art and the claims

(MPEP 2141.02)

Breithbarth does not teach microparticles to comprise silica particles coated with alumina, and their size to be about 500 nm or less. However, Breithbarth does teach the silica particles may be coated with an active phase on the silica particle's surface (column 3, lines 20-22). Also, Tan et al. teach silica-coated nanoparticles, wherein the nanoparticles comprise a core coated with a shell, such as mixtures or layers of silica and alumina, and derivatized with functional groups on the surface thereof, which can be used as drug molecule particles (Figure 1; column 2, lines 9-14 and 24-25; column 5, lines 55-60 and 67; column 6, lines 1-4 and 36-44; and column 11, line 62 through column 12, line 1). Tan et al. further teach that the nanoparticles are preferably between about 10 nm to about 300 nm (column 4, lines 26-35), because the small size allows nanoparticles to be exploited to produce a variety of products, such as therapeutics (column 1, lines 29-34), and can be dispersed in a pharmaceutically acceptable carrier and administered to a patient (column 12, lines 1-4).

It is noted by the examiner that Breithbarth does not explicitly teach the zeta potential being about 40 mV or more. However, Breithbarth teaches that the qualities of the ideal particles are dependent on their very small size, electrical potential, zeta

potential, uniformity, spherical shape and rigid nature and their good flow properties (column 2, lines 36-39). Breithbarth further teaches that the microparticles preferably have a substantial negative charge at physiological pH and physiological ionic strength (column 3, lines 1-3). Therefore, in the absence of evidence to the contrary, the particles of Breithbarth would inherently possess a zeta potential of about 40 mV or more.

Finding of *prima facie* obviousness

Rational and Motivation (MPEP 2142-43)

Therefore, it would have been *prima facie* obvious for one skilled in the art at the time of the invention to use silica and alumina-coated nanoparticles in the place of the silica microparticles of Breithbarth, because Tan et al. teach the nanoparticle size is preferred for exploiting the small size.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nathan W. Schlientz whose telephone number is 571-

272-9924. The examiner can normally be reached on 8:30 AM to 5:00 PM, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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